Abstract of dissertation entitled

“An evidence-based protocol for Therapeutic Hypothermia to improve neurological outcomes for neonates with Hypoxic-Ischemic Encephalopathy in a Neonatal Intensive Care Unit”

Submitted by

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Perinatal hypoxic-ischemic encephalopathy is one of the leading causes of mortality and severe neurological disability in children below five years of age. In the past, supportive treatment aimed to correct organ dysfunctions and maintain physiological homeostasis in these patients, but there had not been any proven therapy to improve their clinical outcomes yet. Recently, researches have focused on the prevention of the brain injury caused by hypoxic-ischemic encephalopathy by means of therapeutic hypothermia. Such innovation has led to a significant reduction in the composite primary outcome of death or major neurodevelopmental disability at 18 months after hypoxic-ischemic encephalopathy, including neonates who suffered from birth asphyxia.

The aim of this dissertation is to adopt the evidence-based innovation in Hong Kong. A literature review has been conducted on the currently available evidence regarding therapeutic hypothermia in neonates with perinatal hypoxic-ischemic encephalopathy who are at or above 35 weeks of gestation. Methods of administering therapeutic hypothermia, the selection criteria for eligible candidates, and the feasibility of transferring the overseas practices back to Hong Kong will be covered and based on
the practices adopted in the overseas studies. This essay serves to introduce the evidence-based intervention, by means of whole-body hypothermia or selective head cooling, into a local Neonatal Intensive Care Unit (NICU), with a view to improving the survival and long-term neurological outcomes for neonates with HIE.
An evidence-based protocol for Therapeutic Hypothermia to improve neurological outcomes for neonates with Hypoxic-Ischemic Encephalopathy in a Neonatal Intensive Care Unit

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A dissertation submitted in partial fulfillment of the requirements for the Degree of Master of Nursing at The University of Hong Kong.

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**Declaration**

I declare that the dissertation thereof represents my own work, except where due acknowledgement is made, and that it has not been previously included in a thesis, dissertation or report submitted to this University or to other institution for a degree, diploma or other qualifications.

Signed………………………………………………..

Leung Yin Ling
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# Table of Contents

*Declaration* ................................................................................................................................. i
*Acknowledgements* ........................................................................................................................ ii
*Table of contents* ............................................................................................................................. iii

**Chapter 1: Statement of the Problem** ........................................................................................... 1
  Background ........................................................................................................................................ 1
  Affirming the Need ............................................................................................................................ 2
  Objectives and Significance ............................................................................................................... 4

**Chapter 2: Review of Evidence** ...................................................................................................... 6
  Search and Appraisal Strategies ........................................................................................................ 6
  Results .............................................................................................................................................. 8
  Description of studies ....................................................................................................................... 8
  Summary and Synthesis .................................................................................................................... 17
  Summary of the Evidence ................................................................................................................ 21
  Implications for practice .................................................................................................................. 22

**Chapter 3: Implementation Potential** ............................................................................................ 23
  Target Population and Setting .......................................................................................................... 23
  Transferability of the Findings ......................................................................................................... 24
  Feasibility ....................................................................................................................................... 27
  Cost-Benefit Analysis of the Innovation ......................................................................................... 31

**Chapter 4: Evidence-based Practice Guideline** .......................................................................... 34
  Overview of guidelines .................................................................................................................... 34
  Recommendations ......................................................................................................................... 35

**Chapter 5: Implementation Plan** .................................................................................................. 39
  Communication Plan ........................................................................................................................ 39
  Initiating the changes ....................................................................................................................... 41
  Sustaining the Change Process ...................................................................................................... 42
  Pilot Testing .................................................................................................................................... 43

**Chapter 6: Evaluation Plan** .......................................................................................................... 44
  Intervention Outcomes and Outcome Measurements .................................................................. 45
  Nature and Number of Clients Involved ......................................................................................... 46
  Data Analysis ................................................................................................................................. 47
  Criteria for Effectiveness .............................................................................................................. 48
  Conclusion ...................................................................................................................................... 48

*Appendices* ..................................................................................................................................... 50
*References* ..................................................................................................................................... 65
Chapter 1: Introduction

Background

Neonatal death in 2008 contributed to 41% (3.575 millions) of mortality in children below five years old around the world (Lancet, 2010). Birth asphyxia is one of the major causes of death (Black et al., 2010). Neonatal encephalopathy due to perinatal hypoxic-ischemic insult not only causes death but also brain injury which leads to long-term neurological disability (Vannucci, 1990). Hypoxic-ischemic encephalopathy (HIE) results in a variety of major neurological morbidity, varying from cerebral palsy, cognitive impairment, developmental delay or learning difficulties, impaired vision or blindness, deaf or hearing impairment, gross motor and coordination impairments, to epilepsy (Mwaniki, Atieno, Lawn and Newton, 2012). The risk of the affected child suffering from multiple impairments is around 20%. Not only the individual suffers, there is also a great burden on the family and the society (Mwaniki et al., 2012). Despite advancements in obstetrical and neonatal care which have improved the survival rate, the chances of developmental disabilities have not declined greatly (Ferriero, 2009).

“Perinatal hypoxic-ischemic encephalopathy is a subset of neonatal encephalopathy” (Higgins et al., 2011). The definition of perinatal refers to the hypoxic or ischemic insult caused by an acute brain injury which occurs in the prenatal, intrapartum, or postpartum period” (Shankaran, 2005). According to American College of Obstetricians and Gynecologist and American Academy of Pediatrics (2003), it refers to the term infant having a disturbed neurological function in the earliest day of life which manifested by difficulty in initiating and maintaining
respiration, depression of tones and reflexes, subnormal level of consciousness, and often seizure.

There was no definite therapy except providing supportive treatments for perinatal hypoxic-ischemic encephalopathy. In the past, correcting organ dysfunction, which included treating hypotension, hypoventilation, electrolyte imbalances and seizures, was the main medical focus (Shankaran & Laptook, 2007). Recent researches have focused on the prevention of the brain injury caused by hypoxic-ischemic encephalopathy by means of therapeutic hypothermia. In order to reduce cerebral injury, body temperature of the neonate is reduced by 3°C to 5°C below the normal body temperature. Although the pathway of cerebral injury in term infants with HIE is not exactly clear, it is believed that hypothermia may block the biomedical pathways, inflammatory cascades and self-repair process which lead to further damage and death of neuronal cells.

**Affirming the Need**

From the previous randomized controlled trials, there was evidence showing the association of using therapeutic hypothermia with the reduction of death or disability in infancy and childhood (Shah, 2010), and is a safe procedure to be applied in clinical practice. However, around 40%-50% of infants treated with hypothermia still die or suffer from significant neurological disability (Edwards et al., 2010). Many knowledge gaps remain unclear. Controversies exist and no international consensus has been reached. Therefore, it is necessary to refine the current hypothermia treatment protocols.
As a tertiary center in neonatal intensive care, our unit receives referrals of infants suffering from perinatal hypoxic-ischemic encephalopathy from both the public and private hospitals. We are at the forefront of the battle against time, as delayed treatment is associated with worse clinical outcomes. Therefore, an evidence-based protocol is urgently needed, followed by establishing a team of well-trained professions to take care for this group of patients, so as to increase the effectiveness and the standard of care once we encounter them.

According to the data from a hospital in Hong Kong, among 3500 newborns between the year 2011 and 2012, 4-5 neonates suffered from perinatal hypoxic-ischemic encephalopathy (L.Y. Ko, personal communication, August 2, 2013). Nearly 50 percent of them died of multi-organ failure. The survivors developed developmental disabilities.

There are longitudinal studies investigating the long-term outcome of applying therapeutic hypothermia on newborn infants with HIE. A study from Shankaran et al. (2012) performed a follow-up on the previous trial’s participants at six to seven years old, looking at their neurological outcomes. It showed that therapeutic hypothermia could decrease the death rate, with no increase in the rate of severe disability among the survived participants. Because the treatment methods of therapeutic hypothermia on neonates with hypoxic-ischemic encephalopathy continue to develop, before contemplating the implementation of therapeutic hypothermia in our unit, a thorough review should be performed on the current literature, such that we may adhere to the international recommendations if any. The clinical question is, are there any measures to maximize patients’ safety and outcomes?
Therapeutic hypothermia uses a sophisticated machine to reduce neonates’ body temperature by 3°C to 5°C below the normal body temperature in order to reduce cerebral injury. Therapeutic hypothermia should be offered to infants with moderate to severe HIE under clearly defined protocols (Perlman et al. 2010). National Institute for Health and Clinical Excellence (2010) and the latest Neonatal Resuscitation Program (NRP) guidelines (2010) stated that therapeutic hypothermia could only be performed on infants with perinatal asphyxia who meet the preset criteria by trained professional, and could only be provided by the centers that are equipped with specialized programs and advanced facilities.

Through developing an evidence-based clinical care pathway on therapeutic hypothermia for neonates with hypoxic-ischemic encephalopathy, clear and highly organized recommendations can be provided to different healthcare professionals as a reference and guideline in the clinical care of these fragile infants. We have to establish a training program based on the protocol we developed together with sophisticated equipment to improve patients' safety and outcomes.

**Objectives and Significance**

The bedside nurse plays an important character in the management of patients with HIE. Temperature monitoring is crucial in controlling the hypothermia therapy. Therefore, the nurses have to continuously monitor and regulate the degree of cooling and subsequently the change in core body temperature. Besides, they must promptly identify the signs and symptoms of adverse effects the infant may have before and
during hypothermia, such as cardiac arrhythmias, bleeding, skin changes due to cooling, hypotension, and infection.

**Significance**

Neurological outcome is defined as whether the neonate with hypoxic-ischemic encephalopathy developed cerebral palsy, developmental delay which was accessed by Bayley Scales or Griffith developmental assessment, intellectual impairment, blindness (vision impairment <6/60 on both eyes) and deafness which required hearing aids.

**Objectives**

1. To determine the long-term neurological outcomes on newborn infants with HIE undergo therapeutic hypothermia.

2. To determine the mortality rate on newborn infants with HIE undergo therapeutic hypothermia.

3. To determine the empirical evidence on the efficacy of therapeutic hypothermia on the neurological outcomes on newborn infants with HIE undergo therapeutic hypothermia.

4. To ascertain the side effects in newborn infants with HIE undergoing therapeutic hypothermia.

5. To establish an evidence-based protocol of therapeutic hypothermia to improve the neurological outcome for neonates with HIE.
Chapter 2: Critical Appraisal

Search and Appraisal Strategies

Inclusion Criteria

Types of studies

Only randomized controlled clinical trials that compared therapeutic hypothermia (either selective head cooling or whole-body cooling) with normothermia (standard care) to treat newborns with hypoxic-ischemic encephalopathy were included.

Types of participants

Newborns should be equal to or greater than 35 weeks of gestation with birth asphyxia, clinical findings of encephalopathy based on Sarnat staging (Sarnat, 1976), and without congenital abnormalities.

Types of outcome measures

The primary outcome measure was death or long-term major neurodevelopmental disability. The secondary outcome was mortality and the incidence of adverse effects of cooling.

Exclusion Criteria

1. The duration of follow-up was less than 12 months after birth, which could not demonstrate the intervention’s effect on the intermediate neurological outcome.
2. Studies that included infants from multiple RCTs with previously reported data.
3. Uncontrolled case series that with no randomization.
**Literature Search**

A literature search was performed comprehensively to identify all the relevant studies. It includes Pubmed and the Cochrane Central Register of Controlled Trials. The following keywords were used: Infants, Newborn; Asphyxia; Hypothermia; Therapeutic Hypothermia; Hypoxic-ischemic Encephalopathy; Neonatal encephalopathy; Developmental disability; Whole-body Hypothermia; Selective head cooling; Randomized Controlled Trials. Searching on the bibliographies of identified articles was performed to identify additional articles. No language restrictions were applied. The search was last updated on 10\(^{th}\) December 2012. The searching strategies and results were shown on Appendix A and Appendix B showed a flow diagram of the included and excluded studies.

**Data extraction**

All the titles and abstracts that fulfilled the selection criteria were assessed in this review. 6 research studies were selected for this review. A table of evidence was formulated from extracting and summarizing the relevant data from the 6 studies.

**Quality Assessment**

Each selected study was assessed regarding the methods of randomizations, blinding, risk of bias and outcomes reporting. Randomized controlled trials methodology checklist of Scottish Intercollegiate Guidelines Network (SIGN, 2013) was adopted in assessing the internal validity and overall assessment (see Appendix C). Based on the recommendations of the level of evidence, by SIGN (2013), the grade of level of evidence for studies was performed in quality assessment (see Appendix D).
Results

Description of studies

Characteristics of Included Studies

The characteristics of the studies are summarized in Table 2 (see Appendix E).

Demographics

Six randomized controlled trials were identified for evaluation (Shankaran et al., 2005; Gluckman et al., 2005; Azzopardi et al., 2009; Zhou et al., 2010; Simbruner et al., 2010; Jacobs et al., 2011). They were all carried out to compare the effects of applying therapeutic hypothermia versus no cooling in hypoxic-ischemic encephalopathy on mortality and neurological outcomes in the neonatal intensive care unit. The years of publication ranged from 2005 to 2011. They are all multicenter studies, the National Institute of Child Health and Human Development (NICHD) network in North America performed one (Shankaran et al., 2005), one was carried out in China (Zhou et al., 2010) and four studies were from different international centers (Gluckman et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Jacobs et al., 2011). One out of six studies received funding from the private sector. The Olympic Medical supported the study of Gluckman et al. (2005).

Participants

Six randomized controlled trials comprised one thousand and eighty-two newborn infants. Their neurological outcomes at eighteen months of age and/or afterwards were available. Randomization of all the participants to either the intervention group or controlled group was performed, after confirming that they fitted the trials’ inclusion criteria and informed consent was obtained from the parents. Term or late preterm infants were included in the six trials with equal or greater than
37 weeks’ gestation in Zhou et al. (2010). Four out of six trials included newborn infants equal or greater than 36 weeks’ gestation (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010). Jacobs et al. (2011) included newborn infants with equal or greater than 35 weeks’ gestation. All of the included newborn infants presented with moderate or severe encephalopathy and were without congenital abnormalities. As all the six trials were multicenter studies, three out of six trials consisted of outborn infants which were transported to tertiary centers for neonatal intensive care (Shankaran et al., 2005; Zhou et al, 2010; Simbruner et al., 2010).

**Outcome measures**

All the six studies had clearly defined outcomes. Mortality was one of the primary end-points in determining the effects of therapeutic hypothermia on neonates with hypoxic-ischemic encephalopathy in all six studies. The follow-up periods ranged from 18 months in 3 studies (Gluckman et al., 2005; Azzopardi et al., 2009; Zhou et al, 2010), and 18 to 24 months in 3 studies (Shankaran et al., 2005; Simbruner et al., 2010; Jacobs et al., 2011)

In all six studies, neurological examination together with visual and auditory assessments were performed by trained staff in order to determine whether the participants developed long-term neurological disability such as visual impairment or sensorineural deafness that required amplification. The diagnosis of cerebral palsy was also included in determining the neurological outcome. It was reported in all six studies.

Different assessment tools were employed in the studies by trained
professionals in determining the neurological outcomes of neonates with hypoxic-ischemic encephalopathy. There were four studies using the Bayley Scales of Infant Development – Psychomotor Development Index (BSID PDI) for assessing neuromotor development and Bayley Scales of Infant Development – Mental Development Index (BSID MDI) for assessing mental development (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Jacobs et al., 2011). It is a validated and widely used assessment tool to assess global development of infants. It was used in children with age from one to forty-two months (Chaudhary et al., 2013).

Three studies utilized the Gross Motor Function Classification System (GMFCS) (Gluckman et al., 2005; Azzopardi et al., 2009; Jacobs et al., 2011). Gross Motor Function Classification System is used to grade cerebral palsy children on their gross motor functions with five level of classification (Palisano et al., 1997). It provides a method to quantify the performance of the children on standing, sitting and walking ability. The use of mobility aids is also graded. The Cerebral Palsy population registries routinely collect GMFCS level data as part of the standard dataset (Morris, 2008). Palisano et al. (1997) defined Gross Motor Function Classification level 1 as the mildest impairment and level 3-5 as severe neuromotor disability which mean infants who have limitation in walking, apply supportive devices to lower back during sitting or limited or severe self mobility problem.

Two studies used the Development Quotient (DQ) (Simbruner et al., 2010; Zhou et al, 2010). It is one of the most commonly used tools for global development assessment. The psychomotor development of children within twenty-four months of life could be assessed. It includes six domains of functioning (locomotors, personal/social, hearing and speech, eye and hand coordination, performance and
practical reasoning) (Chaudhary et al., 2013; Luiz, Foxcroft, & Stewart, 2001).

**Characteristics of Included Interventions**

*Interventions*

In all six studies, therapeutic hypothermia was started within six hours after birth. Although three out of six trials included outborn infants requiring transportation to the tertiary centers for neonatal intensive care (Shankaran et al., 2005; Simbruner et al., 2010; Zhou et al, 2010), the randomization was promptly performed and the intervention could still commence by six hours after birth.

Two modes of hypothermia strategy were employed in the six randomized controlled trials including selective head cooling and whole-body hypothermia. Two out of six studies used selective head cooling to perform therapeutic hypothermia (Gluckman et al., 2005; Zhou et al, 2010) while other four studies used whole-body hypothermia (Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Jacobs et al., 2011).

The duration of hypothermia in all six studies was 72 hours (Shankaran et al., 2005; Gluckman et al., 2005; Azzopardi et al., 2009; Zhou et al, 2010; Simbruner et al., 2010; Jacobs et al., 2011).

After the administration of therapeutic hypothermia, it was followed by the process of rewarming. In four studies, it took four hours to rewarm infants, increasing the body temperature by 0.5°C per hour (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010). Jacobs et al. (2011) rewarmed
infants by increasing 0.5°C every second hour with total rewarming duration of eight hours. One study by Zhou et al. (2010) rewarmed infants spontaneously at room temperature which took 12 hours to finish rewarming process.

**Characteristics of Adverse Effects of the Included Interventions**

*Adverse effects*

There were different kinds of adverse effects of using therapeutic hypothermia on hypoxic-ischemic encephalopathy infants reported among the six selected studies. The main adverse effects from the six studies could be grouped as several groups including cardiovascular, hematological adverse effects and hepatic dysfunction (see Appendix F). The detail results will be discussed in the following section.

**Results of the Review**

The effect sizes of all the outcomes were calculated in terms of odds ratio. The details are presented in Table 2 (see Appendix E).

The rate of death and severe disability after 18 months is the primary outcome for all six studies. The odds ratio of all studies on this outcome ranged from 0.21 to 0.73. It demonstrated a significant reduction in the risk of death and disability in newborn with hypoxic-ischemic encephalopathy who underwent therapeutic hypothermia. The findings achieved statistical significance in four out of six studies (Shankaran et al., 2005; Simbruner et al., 2010; Zhou et al, 2010; Jacobs et al., 2011).

The secondary outcome of all six studies was rate of death. All of them demonstrated that infants with hypoxic-ischemic encephalopathy who underwent
therapeutic hypothermia were having lower risk to die than those received standard care. Their odds ratio ranged from 0.53-0.93. Two of the studies (Shankaran et al., 2005; Jacobs et al., 2011) showed a statistically significant reduction in death in the cooling group.

There are five studies reporting the effect of therapeutic hypothermia on death or major disability at 18-24 months of age according to the severity of baseline encephalopathy (Gluckman et al., 2005; Shankaran et al., 2005; Simbruner et al., 2010; Zhou et al, 2010; Jacobs et al., 2011). Therapeutic hypothermia was associated with a reduction in death or major disability on moderate encephalopathy infants. The odds ratio of this outcome ranged from 0.31-0.63. Three of the studies were statistically significant (p<0.05) in the reduction in death or major disability on moderate encephalopathy infants (Gluckman et al., 2005; Shankaran et al., 2005; Zhou et al, 2010). For infants with severe encephalopathy, there was a study showing no improvement in mortality or major disability despite applying therapeutic hypothermia (Gluckman et al., 2005). However, four studies showed a reduction in death or major disability on severe encephalopathy infants (Shankaran et al., 2005; Simbruner et al., 2010; Zhou et al, 2010; Jacobs et al., 2011). The odds ratio ranged from 0.17-0.63. The studies from Simbruner et al. (2010) and Zhou et al. (2010) achieved statistically significance among severe encephalopathy infants.

Azzopardi et al. (2009) and Jacobs et al. (2011) reported that among the surviving infants at 18 to 24 months of age, there was an association with an increase in survival without neurological abnormality with therapeutic hypothermia treatment. Azzopardi et al. (2009) defined it as normal vision and hearing, no cerebral palsy was
developed when survived, and both the mental developmental index and the psychomotor index of a score of 84 or more. The survival without neurological abnormality from Jacobs et al. (2011) was defined as no neuromotor delay which the baby has no Cerebral palsy or they have Gross Motor Function Classification System disability level of 0 and a BSID-II Psychomotor Development Index of greater than \(-1\) SD or a BSID-III Motor Composite Scale score of greater than \(-1\) SD. Also the baby has no developmental delay, their BSID-II Mental Development Index score of greater than \(-1\) SD or BSID-III Cognitive and Language Composite Scale scores of greater than \(-1\) SD), no blindness, and no deafness is found.

The odds ratio were 2.0 and 2.24 respectively which showed that infants undergoing therapeutic hypothermia had 2 to 2.24 times more chance to survive without neurological abnormality (Azzopardi et al., 2009) and Jacobs et al., 2011). Both of the results were statistically significant.

There were different kinds of adverse effects of using therapeutic hypothermia on hypoxic-ischemic encephalopathy infants reported among the six selected studies. The main adverse effects from the six studies were extracted. Their effect sizes were calculated and listed in Table 3 (see Appendix F). They could be grouped as several groups including cardiovascular, hematological adverse effects and hepatic dysfunction. For cardiovascular adverse effects, three studies reported the infants suffered from cardiac arrhythmia with sinus bradycardia, heart rate<80 beats/min during cooling (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009). They showed that applying cooling on infants with hypoxic-ischemic encephalopathy had 2 to 10 times the risk of developing cardiac arrhythmia compared to infants who
did not receive cooling. Medical interventions had to be taken, and cooling had to be stopped occasionally. This achieved statistical significance in the study by Gluckman et al., 2005.

For the adverse effects on hypotension, studies of Gluckman et al. (2005), Shankaran et al. (2005), Azzopardi et al. (2009), Simbruner et al. (2010), Jacobs et al. (2011) reported that the infants had hypotension on both intervention and control group with mean blood pressure (MAP) <40mmHg. Some infants required inotropes support to maintain the blood pressure (Shankaran et al., 2005; Jacobs et al., 2011). 3 out of 5 studies showed there was 1-1.5 times higher risk for hypothermia infants to develop hypotension than normothermia infants (Gluckman et al., 2005; Shankaran et al., 2005; Simbruner et al., 2010). However, no result yielded statistical significance.

There was one study from Jacobs et al. (2011) showing that the application of therapeutic hypothermia on HIE infants had around 3 times the risk of causing prolongation of the QT interval than infants not receiving hypothermia. It also achieved statistical significance.

For haematological adverse effects, developing thrombocytopenia was reported among hypothermia group with platelet count below 150x10^9/L among four out of five studies (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Jacobs et al., 2011). Therapeutic hypothermia group had 1.3-3 times the risk of developing thrombocytopenia compared to non-cooling infants. No statistical significance was shown among the studies.
The infants also suffered from coagulopathy (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Jacobs et al., 2011). Three out of five studies reported around 1.4-1.8 times of developing coagulopathy than normothermia infants (Gluckman et al., 2005; Shankaran et al., 2005; Jacobs et al., 2011). No statistical significance was shown among the studies.

For hepatic dysfunction, the infants had elevated liver enzymes with AST>200U/L or ALT>100U/L in five studies (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Zhou et al., 2010; Jacobs et al., 2011). There were two out of five studies showing an increased risk of around 1.37-1.61 than non-cooled group to have hepatic dysfunction. The results were not statistically significant.

In summary, there were statistically significant evidence showing an increase in cardiac arrhythmia with sinus bradycardia and prolonged QT interval when the infants underwent therapeutic hypothermia.

**Quality Assessment**

The methodology checklist of the Scottish Intercollegiate Guidelines Network (SIGN, 2013) for randomized controlled trials was used in internal validity and overall assessment (see Appendix C). By following the recommendations of the level of evidence by SIGN (2013) (see Appendix D), the level of evidence for the studies was graded. All the six studies are graded as good quality (1++). Most or all of the criteria could be fulfilled in the methodology checklist for controlled trials (SIGN, 2013).
Table 4 (see Appendix G) and Table 5 (see Appendix H) show the details of quality assessment in internal validity and overall assessment respectively.

**Strengths**

The methodology is strong among the six studies. Four studies used computer-generated numbers in opaque envelopes in the randomization process (Gluckman et al., 2005; Simbruner et al., 2010; Zhou et al, 2010; Jacobs et al., 2011). Shankaran et al. (2005) performed randomization from a data-coordinating center. Central data-coordinating center or a web-based system was used in Azzopardi et al. (2009) as their method of randomization. In all six studies, the neurological outcome assessors were masked from knowledge of the patients' study group. The neurological outcome assessment in the six included studies followed the survivors to at least 18 months of age.

**Limitations**

In the six trials reporting the neurological outcomes at least 18 months, however the caregivers was not blinded to the intervention due to the nature of the intervention.

**Summary and Synthesis**

There was a beneficial effect demonstrated from the comprehensive review of the selected studies; applying therapeutic hypothermia on neonates with hypoxic-ischemic encephalopathy reduces mortality, improves neurological outcomes and decreases the infants' chance of having major disability when they survive to older months. Through the critical appraisal, some useful information could be retrieved to
develop an evidence-based protocol.

**Characteristics of Interventions Reviewed**

Term or late preterm infants were included in the six trials with equal or greater than 37 weeks’ gestation in Zhou et al. (2010). Four out of six trials included newborn infants equal or greater than 36 weeks’ gestation (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010). Jacobs et al. (2011) included newborn infants with equal or greater than 35 weeks’ gestation. Therapeutic hypothermia showed a reduction in the risk of death and disability in infants with hypoxic-ischemic encephalopathy in the six studies. It is thus recommended that therapeutic hypothermia should be used in newborn infants equal to or greater than 35 weeks of gestation as demonstrated in the studies.

Apart from clinical diagnosis and bedside grading of the severity of hypoxic-ischemic encephalopathy, Gluckman et al. (2005) and Simbruner et al. (2010) performed Amplitude-integrated electroencephalogram (aEEG) recording before randomization to diagnose and stage the baseline encephalopathy. It is recommended to use both clinical staging and Amplitude-integrated electroencephalogram (aEEG) to assess the baseline encephalopathy staging.

**Hypothermia Intervention**

Therapeutic hypothermia consists of 3 phases. They are induction, maintenance and rewarming. Recommendations could be made from the best available evidence among the six studies.
**Types of cooling**

Both whole-body hypothermia and selective head cooling can be used to perform therapeutic hypothermia on neonates with HIE safely.

**Time of Initiation**

All the studies initiated the intervention prior to six hours after birth. No variation of the initiation time was present among the six studies. It is recommended that therapeutic hypothermia should be started within six hours after birth.

**Cooling duration**

The duration of hypothermia in all six studies was 72 hours. It is recommended that the cooling maintaining phase could be 72 hours.

**Rewarming Process**

Although there were variations in the rate of the rewarming process, researchers in four studies that the infants were rewarmed by 0.5°C per hour with four hours rewarming period (Gluckman et al., 2005; Shankaran et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010). Jacobs et al. (2011) rewarmed infants by 0.5°C every second hour with eight hours rewarming duration. One study by Zhou et al. (2010) rewarmed infants naturally at room temperature which took 12 hours to finish the whole rewarming process. Although at present, there was no study to directly compare and find out the optimal method of rewarming, all the six studies applied gradual rewarming which indicated slow rewarming is preferable. Fever or overheating will lead to hyperthermia. It should be avoided to prevent undesired
adverse outcomes. It is recommended that rewarming process could be gradual with no more than 0.5°C per hour until the temperature was normalized, with a total rewarming duration of four to eight hours.

**Nursing care**

In all six studies, intervention was started on infants within six hours after birth. As neuronal injury is irreversible, the earlier is better. Therefore, it is necessary to set up an effective communication system between the labour room of obstetric units and the neonatal resuscitation team for early admission of newborns to NICU. This could facilitate preparation and priming of therapeutic hypothermia equipment once the infants first developed signs of encephalopathy. It can promote early initiation of therapeutic hypothermia, maximizing the benefits as demonstrated in the studies.

All six studies placed the newborn infants in the intervention group in an open incubator. No conventional overhead heater was switched on. This can help achieve rapidly the desired temperature range in therapeutic hypothermia. It is recommended that newborn infants with hypoxic-ischemic encephalopathy should be put in an open incubator and overhead heater should be switched off.

All six studies performed continuous temperature monitoring by either rectal temperature (Gluckman et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010; Zhou et al, 2010; Jacobs et al., 2011) or esophageal temperature monitoring (Shankaran et al., 2005) during therapeutic hypothermia process. It is recommended
that temperature probe should be checked regularly and confirmed in position. The dislodgement of temperature probe may alter the cooling maintenance.

Mild edema, scleroderma or subcutaneous fat necrosis were reported in Gluckman et al. (2005), Shankaran et al. (2005) and Zhou et al. (2010) during therapeutic hypothermia which recovered after rewarming. It is recommended that regular skin assessment is needed to observe the infant’s tolerance during hypothermia treatment. Frequent minimal turning is also recommended for infants undergoing therapeutic hypothermia to prevent pressure sores.

Patient outcome is determined by many factors. Giving a holistic support could help. The bedside nurse also needs to psychologically support the patient’s family, instead of just focusing on the cooling infant. We have to highlight parents' concerns about their baby as well. It is recommended that nurses should provide adequate parent counseling concerning the severity of hypoxic-ischemic injury and the intervention employed.

**Summary of the Evidence**

Six multicenter, randomized controlled trials published from 2005 to 2011 were reviewed. A total of one thousand and eighty-two newborn infants were included. All of the studies investigated the effects of therapeutic hypothermia on infants with hypoxic-ischemic encephalopathy. The results showed their neurological outcomes and survival of 18 to 24 months of age. All the six studies were rated as good quality (1++) in quality appraisal with reference to SIGN (2013). All studies
showed the risk of death and disability in infants with hypoxic-ischemic encephalopathy who underwent therapeutic hypothermia was reduced. Two studies showed a statistically significant effect in reducing mortality in the therapeutic hypothermia group. Two studies reported that among the survived infants to 18 to 24 months of age, there was an association with an increase in survival without neurological abnormality with therapeutic hypothermia treatment (Azzopardi et al., 2009; Jacobs et al., 2011). Although there is evidence showing the occurrence of short-term adverse effects during therapeutic hypothermia, the benefits of therapeutic hypothermia on the survival and neurological outcome can outweigh it. Therefore, the best available evidence suggested that applying therapeutic hypothermia on infants with hypoxic-ischemic encephalopathy will improve neurological outcomes and decrease the infant’s chance of having major disability when they survive into childhood.

**Implications for Practice**

Perinatal hypoxic-ischemic encephalopathy (HIE) disturbed the neurological function of neonates. In the past, only supportive measures could be provided in managing infants with HIE. From the above literature review, it is proven that therapeutic hypothermia is a safe and efficacious rescue therapy in neonates with perinatal hypoxic-ischemic encephalopathy. The neurological outcome among the survivors at 18-24 months follow-up is improved in the six included multicenter randomized controlled trials. Introducing the intervention of therapeutic hypothermia into practice is important. To maximize the benefits, and prevent complications of the intervention, a thorough evidence-based clinical guideline should be established.
Chapter 3: Implementation Potential

Chapter two demonstrated the beneficial effects of administering therapeutic hypothermia on neonates with hypoxic-ischemic encephalopathy, in terms of reducing mortality, improving neurological outcomes and decreasing their chances of developing major disabilities when they survive. The potential of implementing therapeutic hypothermia in a NICU in Hong Kong will be discussed in this chapter. Furthermore, discussions will be made on the transferability of the results summarized from the reviewed studies and the feasibility of introducing it into a NICU. The cost and benefit of launching the therapeutic hypothermia will also be analyzed.

Target audience and setting

Target setting

It is proposed to launch the intervention of therapeutic hypothermia in a NICU in Hong Kong. There are 110 NICU beds in total in Hong Kong, serving as the tertiary centers which receive cases from public and private institutions. They provide sophisticated services for newborn babies including preterm neonates, low birth weight babies, neonates with severe congenital malformations who require urgent medical or surgical interventions after birth, as well as birth asphyxia neonates requiring resuscitation and life-support treatment.

Target population in the proposed setting

The NICU provides life-supporting treatment to neonates suffering from HIE in order to correct their organ dysfunctions. The unit receives HIE neonates who are urgently referred from all public and private hospitals. The proposed intervention,
therapeutic hypothermia, is aimed to reduce mortality of HIE neonates, improve their neurological outcomes and decrease their chances of having major disability when they survive.

Our target population includes all the inborn neonates from home hospital and outborn neonates referred from other hospitals within six hours of life. This time frame is established based on evidence proving that the intervention of therapeutic hypothermia should be initiated within six hours after birth. The target population should be the neonates with equal to or greater than 35 weeks of gestation suffering from perinatal hypoxic-ischemic encephalopathy (HIE) in the proposed setting.

Transferability of the findings

Fitness for the Intervention in the Proposed Setting

In Hong Kong, the neonates suffering from perinatal hypoxic-ischemic encephalopathy (HIE) will be transferred from the labor room to the NICU immediately for resuscitation. The proposed innovation, therapeutic hypothermia will be launched in a NICU in a public hospital in Hong Kong which shares similar settings with the reviewed studies. The settings from the reviewed studies were all Neonatal Intensive Care Unit from the tertiary centers with advanced technology, sophisticated equipment and well-trained health care professionals located in different parts of the world. Such is the case in our proposed NICU in Hong Kong. Newborns from other hospitals can also be transferred to the target setting within 6 hours of birth, which is the therapeutic time window based on the trials.

Similarity
All the reviewed studies are multicenter, randomized controlled trials either from China, North America, or multiple international centers. Although the recruited infants were not of the same ethnicity, the trials all showed similar findings: therapeutic hypothermia could reduce mortality of HIE neonates, improve their neurological outcomes and decreases their chance of having major disability when they survive. This supports the design of this guideline used for a NICU in Hong Kong where Chinese neonates are the major target population. Since perinatal hypoxic-ischemic encephalopathy will occur in neonates with different ethnicity (Black et al., 2010), therefore our target population will also benefit from the proposed intervention.

**Philosophy of Care**

The philosophy of care in a NICU is to provide the best quality care and help the sick newborn to strive for the best outcome. Reducing their mortality, morbidity and enhancing their quality of life are the utmost important objectives in the NICU. According to the most updated evidence available, therapeutic hypothermia can reduce mortality of HIE neonates, improve their neurological outcomes and decrease their chance of having major disability when they survive. The proposed intervention meets the value of the Hospital Authority that “People-centered care” and “Professional Service” and the philosophy of care in the NICU is guided by the values of Hospital Authority. Therefore, the proposed intervention shares the same philosophy of care as the department value.

**Benefiting sufficient clients**

Perinatal hypoxic-ischemic encephalopathy is a global problem which Hong
Kong is not spared. It causes death and also brain injury which leads to long-term neurological disability. In the past, there was no effective therapy except providing supportive treatments and correcting organ dysfunctions. The main medical focus included treating hypotension, hypoventilation, electrolyte imbalances and seizures (Shankaran & Laptook, 2007). From the data of a teaching hospital in Hong Kong where we plan to implement therapeutic hypothermia, although there is only less than 10 neonates annually suffering from perinatal hypoxic-ischemic encephalopathy among 3500 newborns, their mortality and morbidity rate is high with nearly 50 percent died of multi-organ failure while the remaining survivors suffering from developmental disability. The disease adversely affects patients' quality of life and causes a great burden on the family and the health care system. Therefore, both the neonates, the families and even the society shall benefit from the proposed intervention in the long run.

**Time for implementation and evaluation**

A Gantt Chart is designed for presenting the time frame of implementing the proposed intervention. The evaluation period is also included in the chart. The time needed to prepare, implement and evaluate the whole program in the target setting is one year. After obtaining the approval from the Department Head, one month is required for recruiting a working committee and training program facilitators. Four months are needed for pilot testing and one month for revising the program based on the pilot testing. One month is needed to practically prepare for the program to ‘kick off’ which involves finalizing the equipment and manpower arrangement. It is followed by 6 months of full implementation. An extra month will be spent for evaluating the whole program. The Gantt Chart of the program is shown in Appendix I.
Feasibility

A) Strong learning organizational climate

Evidence-based practice is advocated in the medical and nursing fields. More and more studies are being performed to analyze the best methods to improve the nursing care. Our target hospital is a teaching hospital in Hong Kong. There are extra resources to adopt new innovations which can improve the quality of care, as long as such implementation is backed up by carefully reviewed and up-to-date evidence available. There is also a strong learning culture in the target setting. The Nurse Specialists in the target setting, NICU, are responsible for conducting researches and advocating evidence-based practice among other nurses in the ward. Besides, there are regular seminars held for nurses and doctors to share their experiences after overseas training. Speakers from overseas are also regularly invited to share their practices and advancements. This scholarly climates facilitates the implementation of an advanced program such as therapeutic hypothermia. Furthermore, understanding the department's future plan after discussing with the Department head could help the success rate of getting the new innovation approved. The efficacy of the proposed innovation, analysis of its cost-benefits reports will be handed in to illustrate the potential benefits of launching the new intervention. Therefore, it is feasible to launch the intervention of therapeutic hypothermia in the target setting.

B) Possible obstacles

Social and organizational barriers are one of the major obstacles when implementing the innovation. The obstacles could be the lack of support from administrators, or disagreement among clinicians to support such change. There is a natural tendency for one to have hesitation over any unconventional practice, as well
as skepticism over how evidence will improve patient outcomes, or misconception regarding the time and efforts required to implement a seemingly drastic change in practice.

C) Possible solution

It is necessary to seek approval from the Chief of Service before implementation of any program. Therefore, we must explore the stakeholders’ opinions and resistance to change in the beginning. The stakeholders include the Chief of Service (COS), Department Operation Manager (DOM), ward managers, paediatricians, advance practice nurses, and other clinical staffs. A formal meeting will be arranged with the ward manager (WM) and senior nursing staff who control the manpower and resources involved in the implementation of the protocol. A presentation of evidences from the researches and literature reviews could arouse their awareness of such a program and its benefits, as well as the need to change our current practice.

Illustrating the potential benefits may help convince the management to make a change, however, in the beginning of the project, we will also need to explore the economic and workload impact of the program. Related supporting documents including evidence of the efficacy of the proposed intervention and its cost-benefits analysis should be provided for the consideration of the administrators. After that, the details of implementing the innovation such as the manpower, the equipment and costs, the training program and the schedule of the implementation and evaluation will then be discussed.

Paediatricians are the major stakeholders as they are have a duty of care
towards neonates suffering from birth asphyxia, as well as their parents. They will play an active and important role in the implementation. They will help present the evidence-based guideline to the management, as well as explain the practical procedures to healthcare providers of the other disciplines. Doctors and nurses from local or overseas centers who have experience in therapeutic hypothermia may also be invited to share their experiences, practical tips and pitfalls during the implementation of such treatment protocol. The CritiCool Company sponsors the costs of inviting the experienced professionals for sharing.

D) Resources available

All of the nursing staff in the unit will be involved. There are a total of 50 nursing staff in the unit, including 1 Nurse Consultant (NC), 1 Nurse Specialist (NS), 2 Nursing Officers (NO), 6 Advance Practice Nurse (APN) and 40 Registered Nurses (RN).

After the planning stage, a sophisticated machine called “Criti-Cool” would be acquired to perform therapeutic hypothermia. An educational leaflet will be prepared to distribute to the parents when their children are suggested to undergo therapeutic hypothermia, illustrating its theory, benefits and risks.

E) Training

It is important to present the information in the right place and at the right time. Therefore, the training sessions shall preferably be held during working hours. As different nurses have different levels of motivation, acceptance and beliefs towards the changing process, the training sessions should not only provide
theoretical and practical input but also promote evidence-based practice and encourage them to change. An EBP mentor who is familiar with the proposed implementation will be responsible for the training sessions. Working committee will be formed including one nurse consultant, one advanced practice nurse (APN), two senior registered nurses and the guideline proposer. Small groups with 4 to 5 staffs in a group will be divided to promote discussion and interaction. The guidelines with relevant photos and videos of the administration method and procedures will facilitate better understanding.

In order to identify beliefs and attitudes about the current and proposed practice changes, peer group discussion is encouraged and anonymous surveys will be conducted. Transition time is needed for the frontline staffs to familiarize themselves with the new intervention.

EBP mentors who have in-depth knowledge and skills in both EBP as well as individual and organizational change strategies are also a key strategy for sustaining the change.

**F) Evaluation**

Both process evaluation and outcome evaluation will be performed. There will be a month of evaluation period after pilot testing. Amendment based on the pilot testing will be made. A regular audit will also performed during the full implementation period. It could ensure the quality of care. Improvements can be made based on the feedbacks from the nursing staff and paediatricians.
Cost-benefit ratio of the innovation

Potential risks

Safety is the major concern in this intervention. The time of initiation and the degree of cooling has to be continuously monitored accurately as it will affect the effectiveness of the intervention. The neonates undergoing therapeutic hypothermia may develop adverse effects such as cardiac arrhythmia such as sinus bradycardia and prolonged QT interval. Therefore, all the physicians and nurses should follow the guideline strictly in order to achieve the targeted effect which lower the mortality rate and improve neurological outcomes, while minimizing the possible side effects.

Potential benefits

Therapeutic hypothermia is proven to improve the prognosis of a neonate with hypoxic-ischemic encephalopathy. It could not only decrease the mortality but also the permanent neurodevelopmental disabilities in the individuals. The devastating effects on the family, society and economy is also be relieved to a certain degree.

Risks of maintaining current practice

Currently, health care professionals can only offer conventional supportive treatment to the neonates suffering from hypoxic-ischemic encephalopathy if the intervention of therapeutic hypothermia could not be introduced in the target setting. The neonates have a high chance of mortality or suffer from severe irreversible neurological damage.

Costs of implementing the innovation
The major material costs for this intervention comes from buying the new cooling machine and its accessories. A non-invasive device called CritiCool will provide hypothermia to the target patients. It could sense patients’ core temperature by a temperature probe connected to patient’s rectum and skin temperature could be shown by connecting the skin temperature probe. Thermo Wrap, a body shaped garment is connected to the CritiCool to provide the thermal effects. It is a material that is durable and can fit a baby’s body. The targeted cooling temperature could be achieved by modifying the temperature of water circulating between the CritiCool and Thermo Wrap according to the patient’s skin and core temperature. The latter is a consumable item. Each patient has his or her own Thermo Wrap. The set up cost for launching therapeutic hypothermia is estimated to be $174260. It includes the cost of CritiCool (Cooling Control Unit), reusable temperature sensors, connecting water tubings (2 by 2 way Metal Connector), infant Thermo Wrap (12 Units) together with printing costs of the education leaflets and training cost. According to data from 2012, there were 5 to 6 neonates suffering from hypoxic ischemic encephalopathy in the hospital. A calculation of the cost of setting up the program over 2 years sums up to $173106. A detailed table is attached in Table 6 showing the budget estimation of launching the proposed program in the target setting.

Table 6

<table>
<thead>
<tr>
<th>Implementing the innovation</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Set up cost:</strong></td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>$138000</td>
</tr>
<tr>
<td>CritiCool (Cooling Control Unit) + Reusable Temperature Sensors and connecting water tube 2 by 2 way (Metal Connector) + Infant Thermo Wrap (12 Units)</td>
<td></td>
</tr>
<tr>
<td>Training *</td>
<td>$ 20246</td>
</tr>
<tr>
<td>$ 363 x 2hrs x 1 NC= $726</td>
<td></td>
</tr>
<tr>
<td>$ 280 x 2hrs x 1 NS= $560</td>
<td></td>
</tr>
<tr>
<td>$ 280 x 2hrs x 2 NO= $1120</td>
<td></td>
</tr>
<tr>
<td>$ 280 x 2hrs x 6 APN= $ 3360</td>
<td></td>
</tr>
<tr>
<td>$181 x 2hrs x 40 RN = $14480</td>
<td></td>
</tr>
<tr>
<td>Educational Leaflets</td>
<td>$30</td>
</tr>
<tr>
<td>$10 (each language version, 10 sets) x 3</td>
<td></td>
</tr>
<tr>
<td>Running cost each year:</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Educational Leaflets</td>
<td>$10 (each language version, 10 sets) x 3</td>
</tr>
<tr>
<td>Training new staff</td>
<td>$140 x 2hrs x 10 RN</td>
</tr>
<tr>
<td>Consumables (Thermo Wrap)</td>
<td>$2000 x6</td>
</tr>
<tr>
<td>Total cost:</td>
<td></td>
</tr>
</tbody>
</table>

* The mean salary of each rank calculates the hourly pay.

**Potential cost saving with implementation of the innovation**

More information is needed to calculate the cost-effectiveness of implementing therapeutic hypothermic on neonates with hypoxic-ischemic encephalopathy in the local setting. Although there is currently no such data in Hong Kong, there was a study by Regier et al. (2010) supporting its cost-effectiveness. It synthesized the data from the three major randomized controlled trials: the CoolCap trials, National Institute of Child Health and Human Development (NICHD) and Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY). In its statistical analysis, assuming there are 15 infants per year requiring cooling, the costs used on cooling group vs standard care group are £16829 vs £18537. The effectiveness is much higher in cooling group 0.54 (0.49-0.64) than standard care group 0.35 (0.28-0.42). The study also showed that although cooling initially increased the cost, it would be balanced over the first 18 months since birth and the cost-effectiveness would substantially increase if the time horizon were extended to 18 years. Nevertheless, local configurations of neonatal services and future demands for cooling should be considered when interpreting the study findings.

**Conclusion**

Therapeutic hypothermia has been proven to improve neonatal mortality and long-term outcomes in overseas trials. The introduction of such innovation into Hong Kong requires careful review of the current evidence and practical estimation of manpower, time frame and costs. After affirming the feasibility of therapeutic
hypothermia, multidisciplinary efforts will be made to create a protocol in order for staff to adhere to the evidence-based practice in the target setting: From patient selection, to cooling and then re-warming process, so as to maximize the derived benefits and minimize the associated risks.

Chapter 4: Evidence-based Practice Guidelines

Overview of the guidelines

Guideline Title

An evidence-based protocol of therapeutic hypothermia to improve neurological outcome for neonates with hypoxic-ischemic encephalopathy.

Aims of the protocol

The aim of this guideline is to set up therapeutic hypothermia in a Neonatal Intensive Care Unit for neonates with perinatal hypoxic-ischemic encephalopathy based on the best available evidence.

Objectives of the Protocol

- Summarize the clinical evidence for therapeutic hypothermia on neonates with perinatal hypoxic-ischemic encephalopathy
- Formulate the clinical practice guidelines for applying therapeutic hypothermia on neonates with perinatal hypoxic-ischemic encephalopathy based on the best available evidence
- Standardize the procedure of therapeutic hypothermia for perinatal hypoxic-ischemic encephalopathy in the Neonatal Intensive Care Unit

Target Group
The target population is all the neonates with equal or greater than 35 weeks of gestation from home hospital and outborn neonates referred from other hospitals within six hours of life who suffer from perinatal hypoxic-ischemic encephalopathy (HIE).

**Recommendations**

Based on the Scottish Intercollegiate Guidelines Network (SIGN, 2013), the level of evidence (Appendix B) and the grade of the Recommendation were given accordingly (Appendix B). The Recommendations were derived from six reviewed studies.
Recommendation 1.0: Selection Criteria

Newborn infants should be equal or greater than 35 weeks of gestation.

Evidence:

Equal or greater than 37 weeks of gestation (Zhou et al., 2010) (1++)
Equal or greater than 36 weeks of gestation (Gluckman et al., 2005; Shankaran et al., 2005, Azzopardi et al., 2009; Simbruner et al., 2010) (1++)
Equal or greater than 35 weeks of gestation (Jacobs et al., 2011) (1++)

Hypothermia Intervention

Recommendation 2.0: Timing of initiation

Initiate cooling as soon as the neonate is recognized to be suffering from hypoxic-ischemic encephalopathy.

Do not delay beyond the therapeutic window, which was defined as 6 hours of birth in the current neonatal trials.

Evidence:

Therapeutic hypothermia was started within six hours of birth. (Gluckman et al., 2005; Shankaran et al., 2005, Azzopardi et al., 2009; Simbruner et al., 2010, Zhou et al., 2010; Jacobs et al., 2011) (1++)

Recommendation 3.0: Cooling duration

The cooling duration should last for 72 hours.

Evidence:

The neonates were cooled to the target temperature either by whole body hypothermia or selective head cooling for 72 hours before rewarming.
Recommendation 4.0: Rewarming process

A slow rewarming process is required, during which the body temperature is raised by 0.5°C every 2 hours over an 8-to-12-hour rewarming period.

Evidence:
Rewarming of no more than 0.5 °C per hour until normal temperature range (35.5-37.5 °C) (Gluckman et al., 2005; Shankaran et al., 2005, Azzopardi et al., 2009; Simbruner et al., 2010) (1++)
Spontaneous rewarming the neonates in room temperature was used to normal body temperature. (Zhou et al., 2010) (1++)
Rewarming with increasing 0.5°C every 2 hours over 8 to 12 hours. (Jacobs et al., 2010) (1++)

Monitoring

Recommendation 5.0: Nursing assessment

Continuous nursing assessments include vitals signs, neurological observations and skin conditions are essential to observe the infant’s tolerance to the cooling treatment.

Evidence:
Minor cardiac arrhythmia (sinus bradycardia) is noted among neonates under therapeutic hypothermia. (Gluckman et al., 2005; Shankaran et al., 2005, Azzopardi et al., 2009; Simbruner et al., 2010) (1++)
Hypotension is noted among neonates under therapeutic hypothermia. (Gluckman et al., 2005; Azzopardi et al., 2009; Simbruner et al., 2010) (1++)

Some neonates required inotropes or vasopressor support. (Shankaran et al., 2005; Jacobs et al., 2011) (1++)

The neonates developed seizure when having therapeutic hypothermia. (Gluckman et al., 2005; Simbruner et al., 2010) (1++)

Erythema, sclerema (hardening of subcutaneous tissue), cyanosis and subcutaneous fat necrosis was found during therapeutic hypothermia. (Shankaran et al., 2005) (1++)

**Recommendation 6.0:**

**Control the temperatures strictly during cooling. The skin temperature and the rectal or esophageal temperature should be continuously monitored. Prevent the dislodgement of the temperature probe. Minimize the fluctuation of body temperature out of the targeted range.**

**Evidence:**

There were reported difficulties in temperature control during cooling with over cooling and over rewarming. (Gluckman et al., 2005) (1++)

In neonates with severe hypoxic-ischemic encephalopathy, their temperature regulation is poor. (Simbruner et al., 2010) (1++)

Slightly overshoot below the target cooling temperature range was common even when a servomechanism was used. (Jacobs et al., 2011)(1++)
Chapter 5: Implementation Plan

The literature review showed that the application of therapeutic hypothermia on neonates with hypoxic-ischemic encephalopathy could reduce their mortality, improve their neurological outcomes and decrease their chances of developing major disabilities when they survive. The innovation is transferable and feasible to implement in the NICU in Hong Kong as mentioned in the previous chapter. In the following chapters, detailed discussions will be made on the communication plan, the pilot study and the evaluation plan in order to implement the evidence-based practical guideline successfully.

Communication Plan

Identification of stakeholders

The support from the stakeholders is important to the implementation of the evidence-based guideline. The stakeholders of the proposed guideline include the Chief of Service (COS), Department Operation Manager (DOM), Ward Managers (WMs), paediatricians, Advance Practice Nurses (APNs), and other clinical staff of NICU. Exploring the stakeholders’ opinions, concerns and any resistance to change will carry determinative influence on the program implementation.

Communication Process

After identifying the stakeholders, we should formulate a communication plan in order to gain their support. A communication team will be set up. The communication team includes seven people: DOM, WM, 1 paediatrician, NS, APN, a senior nursing staff and the proposer. Both medical and nursing staff will be involved in the team so as to promote multidisciplinary team communication. Paediatricians are the major stakeholders as they are have a duty of care towards neonates suffering
from birth asphyxia. They will play an active and important role in the implementation of the proposed intervention. It takes approximately one month to form a team.

To illustrate the needs of changing current practice on managing neonates with hypoxic-ischemic encephalopathy, a formal meeting within the communication team members will be held for the proposer. The latest evidence from the literature on the potential benefits on the neonates will be presented. It gives the communication team a clear vision on why it is necessary to make changes. The possible resistance on manpower management, budget planning on the equipment and cost, training program, schedule of the implementation and obstacles of launching the innovation will be discussed. Through the formal meeting, the participants in the communication team can have a general understanding of the proposed intervention. The aim of the formal meeting is to get the consensus and the support from the communication team. After collecting team members' points of interest, feedback and comments, amendment could be made after the formal meeting.

Ad hoc individual meetings will be held with the communication team members within a month to have more detailed discussions on their concerns and preparing the required materials for launching the intervention. Through the individual meetings, we can be more readily identify their beliefs and attitude towards the changes. Information sheets and required monitoring and assessment forms will be prepared during the individual meetings. For the individual meetings with paediatricians, we will prepare printed material on the theory and practical procedures of therapeutic hypothermia for their perusal, which will be given to parents. Further
discussions on budget planning will be conducted with DOM. Eliminating the unnecessary spending and making the expenditure more cost-effective are the main focus in the individual meeting with the DOM. The main discussion focus with the WM of the communication team is to determine how to arrange the manpower in running the program. Besides, patient safety is another concerns of the WM. Certain rules have to be set up to ensure patient safety. The individual meeting with the APN will be focused on helping them to familiarize themselves with the cooling operation and logistics. Besides, their roles in coaching the junior staff during this program will also be emphasized.

Initiating the change

Arrangement about the training sessions

After getting the support and the approval from the Chief of Service (COS) and DOM for launching the innovation in the NICU, we can proceed to the next step: frontline staff training. It is an important process to initiate the change. The staff training includes all medical and nursing staff who works in the NICU. They are the one who take care of the patients. It is their responsibility to understand the new innovation.

A working committee will be formed for intensive training. The main trainer is the guideline proposer who is the EBP mentor. The working committee includes one nurse consultant (NC), one advanced practice nurse (APN) and two senior registered nurses (RN) who will help and support the training sessions. Several 2-hour-long training sessions will be held during working hours. During the training, theories of the proposed innovation, benefits and risks, and evidence-based practice will be
introduced by the EBP mentor. Relevant slides and videos of the procedure will be demonstrated to facilitate better understanding. A well-validated cooling device called “CritiCool” will be used for therapeutic hypothermia, and qualified representatives and proctors from the designing company will be involved in the training. Apart from doctors, it is necessary for nurses to learn how to operate it as well as to troubleshoot. Their roles in applying the innovation on the neonates suffering from HIE will be emphasized. Promoting evidence-based practice in the training session can encourage the staff to make a change.

Time will be given for small groups discussion with four to five members in a group to clarify their misunderstandings, raise their enquires and promote interactions. It takes around two months to finish all the training sessions, and this transition period allows the staff to familiarize themselves with the new intervention.

**Sustaining the change**

Regular audit is required in order to sustain the implementation and improve patients’ outcome. By completing a specially designed questionnaire, it can assess the frontline staff’s compliance to the evidence-based guideline. The APN in the NICU are responsible for the audit. The APN could reinforce the importance of therapeutic hypothermia on neonates with HIE.

Apart from regular audit, EBP mentors who have in-depth knowledge and skills in both EBP as well as individual and organizational change strategies are also a key strategy for sustaining the change. They can help identify barriers to the implementation of therapeutic hypothermia, such as any lack of supporting manpower, in order to make the program sustainable.
Pilot Testing

The next step is to put plans into action. It starts with pilot testing. It is an important step to identify any problems with the program that might exist before implementing it on a larger scale, ultimately to include all the target population.

The program will be piloted in a controlled setting with additional observers. Then we will invite all the program participants to critique different aspects of the program, such as the techniques, facilitators' effectiveness, space, accommodations and other resources required. We will revise the program according to the feedbacks.

Two neonates with equal or greater than 35 weeks of gestation with hypoxic-ischemic encephalopathy who are admitted to the NICU within six hours of life will be recruited into the pilot study. According to the statistics of the hospital, the number of the cases with this specific diagnosis is around 4 to 5 per year, therefore a four-month pilot testing will be held for recruiting enough participants.

The working group is responsible for preparing the required equipment, education information for parents and documents such as consent forms. Although all the staff will undergo a formal training on the intervention, a "Cooling Therapy" folder will be made for quick reference. The evidence-based guideline with diagrams to demonstrate the key steps of the procedure and machine operation, checklists, together with the information for parents will be included.

There will be an evaluation after performing the pilot test. The entire process will be evaluated. The nurse consultant and the APN from the working group will be
responsible for the evaluation of the smoothness of operating of the cooling machine, the time required in cooling and re-warming the neonates, and the techniques of the nursing staff in administrating the intervention. We must ensure that all the nurses can administer therapeutic hypothermia in the way that is stated in the guideline as this will affect patient outcome. For the nurses’ feedback, a questionnaire will be given to the nursing staff to express their opinions and give comments on the innovation (Appendix K). The evaluation will include nurses’ satisfaction with the innovation. The resources that are required in the innovation will be evaluated. The evaluation will start from the beginning of the pilot testing to the end of the test.

It takes a month to revise the program after collecting the comments from the pilot testing. A formal meeting will be held by the working group. Each of the comments will be discussed in order for the department to come up with the best methods in launching the innovation. Another month is needed after revising the program to practically prepare the program to “kick off”. It includes finalizing the equipment and manpower arrangement. After that, there will be a six-month-period for the full implementation of the proposed innovation. An extra month will be spent for evaluating the whole program. The Gantt Chart of the program is shown in Appendix I.

**Chapter 6: Evaluation Plan**

An evaluation plan could assess the effectiveness of the innovation and find out areas for improvement. In the followings chapter, a detailed evaluation plan will be discussed which includes how the innovation will be evaluated regarding the intervention outcomes and outcome measurements. The nature of clients to be
involved and numbers of them will be calculated. Besides, the method of the data analysis will be discussed.

**Intervention Outcomes and Outcome Measurements**

**Patient outcomes**

The primary patient outcome from the review studies was to reduce the rate of death or severe disability at 18 months. As the innovation is to help the infants to improve their neurological outcomes despite the insult from hypoxic-ischemic encephalopathy, it takes a longer time of assessment than days of the NICU stay. With reference to the analyzed studies, the neurological outcome assessment is performed at least 18 months of age. Therefore, a thorough neurodevelopmental assessment by the Neurology team is needed, with regular follow-ups and hearing test. Apart from collecting the neurological outcome data from the follow-up at 18 months of age, we need to obtain the death rates of hypoxic–ischemic encephalopathy sufferers with or without undergoing therapeutic hypothermia. These findings will be recorded on a data collection form.

**Healthcare provider outcomes and system outcomes**

There is a strong relationship between patients and healthcare providers. Patients’ outcome is heavily influenced by the care provided by the healthcare providers. Apart from measuring patients’ outcome, healthcare providers' satisfaction is also an important issue in the innovation. A questionnaire will be delivered to them to assess their feelings and degree of satisfaction towards the innovation (Appendix K).
The success of the innovation also depends on the cost of the innovation and the utilization. We have to honestly examine the burden to our system. The utilization percentage can be determined by the actual number of cases undergoing therapeutic hypothermia, and all the eligible cases (including referrals) per year. It could demonstrate the level of the utilization of the innovation, and find out the causes of inadequate utilization (if any). The expenses including the material cost and the manpower cost will be calculated and reviewed yearly.

**Nature and Number of Clients Involved**

**Eligibility criteria**

All the neonates with equal or greater than 35 weeks of gestation from home hospital and outborn neonates referred from other hospitals within six hours of birth who suffer from perinatal hypoxic-ischemic encephalopathy are eligible for the innovation.

**Sample size calculation**

The reviewed studies of Shankaran et al. (2005), Simbruner et al. (2010), Zhou et al. (2010), Jacobs et al. (2011) demonstrated the rate of death or severe disability at the age of 18 months significantly decreased from 31.9 to 14.9% in newborn with hypoxic-ischemic encephalopathy who underwent therapeutic hypothermia compared with the control group. As the eligible criteria this program is similar to the reviewed studies, the findings of our program should be similar when undergoing the same therapy. If a 15% reduction in the rate of death or severe disability at the age of 18 months proves the treatment is effective, the confidence interval (CI) is 0.95 and the margin of error is assumed as 0.2. By means of statistical
software calculation with CI for one proportion is used, the sample size needed is 12. The estimated time for obtaining the sufficient sample population is around 24 months.

**Data Analysis**

**Data Collection**

When the NICU admitted a patient with neonatal hypoxic-ischemic encephalopathy who meets the eligible criteria, the protocol for cooling therapy will be started immediately. As the timing of initiation will affect patients' outcome, the intervention may be started as soon as verbal parental consent is obtained. The doctors and the nurses will introduce the innovation by explaining the baby’s condition, the need of starting the innovation and the consequence of not having the therapy to the parents with the help of the educational leaflet.

The data will be collected throughout the whole intervention process (Appendix J). Data of the innovation utilization will include the number of cases received the therapy and the total number of eligible cases. The time required in cooling the neonates to the target temperature will be recorded. The temperature in cooling and rewarming process will be recorded hourly. The patients' conditions and their response to the therapy will also be recorded in detail. The parents will be invited to fill in a Parents' Satisfaction questionnaire (Appendix L). After that, a regular follow-up with neurological assessment will be performed at the age of 18 months to assess the neurological outcome of post therapeutic hypothermia patients. Besides, A Staff Satisfaction Questionnaire will be distributed to the healthcare providers for their comments of the intervention (Appendix K).
Data Evaluation

The objective of the evaluation is to determine if therapeutic hypothermia could improve mortality and neurological outcome. It is designed for evaluating all subjects, which have hypoxic-ischemic encephalopathy and have undergone therapeutic hypothermia. The mortality rate and the neurological outcome of the subjects will be collected. Hypothesis testing will be used for analyzing the data. A two-tailed z-test for testing one proportion will be performed. It could demonstrate how therapeutic hypothermia, the new practice, changes the mortality and neurological outcome on the hypoxic-ischemic encephalopathy infants compared with non-treatment group.

Criteria for Effectiveness

Primary Patient Outcomes

As discussed in the previous section on sample size calculation, from the reviewed studies, a 15% reduction in the rate of death or severe disability at the age of 18 months proves that the treatment is effective.

Conclusion

From the reviewed literature, the evidence supports that therapeutic hypothermic can improve the neurological outcome on neonates with hypoxic-ischemic encephalopathy. It is a safe measure which gives positive outcomes and it is the only effective intervention proven to help those sufferers. This measure benefits the neonates, their parents and the healthcare systems. It is worthwhile to implement the innovation in the NICU in Hong Kong after analyzing the costs, benefits and risks. An evidence-based guideline needs to be developed together with a well-designed
protocol with clear instructions, in order to help the NICU to launch the innovation successfully. Communication with stakeholders is another essential element before implementing the innovation. Pilot testing is the following step to identify the problems of the program that might exist before launching it on a full-scale. Further improvements could be made based on the pilot testing. Subsequently the program will be fully launched. An evaluation plan has to be done afterwards to assess the effectiveness of the innovation. By preparing a thorough plan with the pre-assessment, an evidence-based guideline and the post evaluation, we can hope that future neonates suffering from hypoxic-ischemic encephalopathy could benefit from a safe implementation of therapeutic hypothermia.
### Appendix A: Table of the Search Strategies and Results

#### Table 1

<table>
<thead>
<tr>
<th>Search Strategies and Results</th>
<th>Database</th>
<th>Review reference lists of relevant studies</th>
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<td>Pubmed</td>
<td>Cochrane&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Search Date</td>
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<td>10/12/2012</td>
<td></td>
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<td>1. Neonates</td>
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<td>3009</td>
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<tr>
<td>2. Newborn</td>
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<td>15389</td>
<td>---</td>
</tr>
<tr>
<td>3. Asphyxia</td>
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<td>534</td>
<td>---</td>
</tr>
<tr>
<td>4. Hypothermia</td>
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<td>1761</td>
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<tr>
<td>5. Therapeutic Hypothermia</td>
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<td>425</td>
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<td>6. Hypoxic-ischemic Encephalopathy</td>
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<td>---</td>
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<td>7. Neonatal encephalopathy</td>
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</tr>
<tr>
<td>8. Developmental disability</td>
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<td>1172</td>
<td>---</td>
</tr>
<tr>
<td>9. Whole-body hypothermia</td>
<td>392</td>
<td>77</td>
<td>---</td>
</tr>
<tr>
<td>10. Selective head cooling</td>
<td>158</td>
<td>94</td>
<td>---</td>
</tr>
<tr>
<td>11. Randomized controlled trial</td>
<td>431284</td>
<td>---</td>
<td>---</td>
</tr>
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<td>Combine 1 and 5 and 11</td>
<td>152(11)</td>
<td>12(1)</td>
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<tr>
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</tr>
<tr>
<td>Combine 2 and 5 and 7 and 11</td>
<td>58(9)</td>
<td>9(2)</td>
<td>---</td>
</tr>
<tr>
<td>Combine 1 and 9 and 11</td>
<td>30(5)</td>
<td>11(2)</td>
<td>---</td>
</tr>
<tr>
<td>Combine 1 and 10 and 11</td>
<td>12(5)</td>
<td>6(2)</td>
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<tr>
<td>Eliminate Duplicates</td>
<td>17</td>
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</tr>
<tr>
<td>Number of Final Selected Literatures</td>
<td>12</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

<sup>1</sup>: Cochrane Central Register of Controlled Trials (Central)

<sup>*</sup>: Eliminated duplicated studies from two database (Pubmed and Cochrane Central Register of Controlled Trials)
Appendix B: Figure of the Flow Diagram of Included and Excluded Studies

Flow Diagram of Included and Excluded Studies

17 potentially relevant studies identified

7 studies were excluded (Not fulfilling the criteria)
- Outcomes included magnetic resonance imaging findings but not mortality, neurodevelopmental disability or adverse effect
- No pre-defined outcomes were reported
- Study inclusion criteria do not meet the pre-defined definition of peripartum asphyxia
- Studies included infants from multiple RCTs(with previously reported data)

5 studies were excluded
- Pilot studies while the duration of outcome measure were not long on assessing neurological outcome to show the intervention effect (follow-up time ranged from 10 days of life, hospital discharge or at 12 months of age)

6 Randomized control Trials were selected for literature review
Appendix C: Methodology Checklist for Controlled Trials

Methodology Checklist 2: Controlled Trials

Study identification (Include author, title, year of publication, journal title, pages)

Guideline topic: Key Question No: Reviewer:

Before completing this checklist, consider:

1. Is the paper a randomised controlled trial or a controlled clinical trial? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist. If it is a controlled clinical trial questions 1.2, 1.3, and 1.4 are not relevant, and the study cannot be rated higher than 1+

2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: 1. Paper not relevant to key question □ 2. Other reason □ (please specify):

Section 1: Internal validity

In a well conducted RCT study…

<table>
<thead>
<tr>
<th>Section 1: Internal validity</th>
<th>Does this study do it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1 The study addresses an appropriate and clearly focused question</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.2 The assignment of subjects to treatment groups is randomised.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.3 An adequate concealment method is used.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.4 Subjects and investigators are kept ‘blind’ about treatment allocation.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.5 The treatment and control groups are similar at the start of the trial.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.6 The only difference between groups is the treatment under investigation.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.7 All relevant outcomes are measured in a standard, valid and reliable way.</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.8 What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>Yes □ Can’t say □ No □</td>
</tr>
<tr>
<td>1.9 All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).</td>
<td>Yes □ Can’t say □ Does not apply □</td>
</tr>
<tr>
<td>1.10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites.</td>
</tr>
</tbody>
</table>

**SECTION 2: OVERALL ASSESSMENT OF THE STUDY**

2.1 **How well was the study done to minimise bias?**  
*Code as follows:*  
High quality (++): ☐  
Acceptable (+): ☐  
Unacceptable – reject: 0 ☐

2.2 **Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain that the overall effect is due to the study intervention?**

2.3 **Are the results of this study directly applicable to the patient group targeted by this guideline?**

2.4 **Notes.** Summarise the authors’ conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.
Appendix D: SIGN Levels of Evidence and Grades of Recommendation

SIGN GRADING SYSTEM 1999 – 2012

LEVELS OF EVIDENCE

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++ High quality systematic reviews of case control or cohort or studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, e.g. case reports, case series

4 Expert opinion

GRADES OF RECOMMENDATIONS

A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or

A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2+

D Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Good practice points

Recommended best practice based on the clinical experience of the guideline development group
### Table 2: Table of Evidence

<table>
<thead>
<tr>
<th>Bibliographic citation</th>
<th>Study type</th>
<th>Level of Evidence</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shankaran et al., 2005 (NICHD study)</td>
<td>Randomized Controlled Trial</td>
<td>1++</td>
<td>Newborn of ≥ 36 weeks gestation with clinical indicators of HIE, umbilical cord blood pH ≤ 7.0 or base deficit ≥ 16mmol/L during 1st hour after birth or Apgar Scores ≤5 at 10 mins, encephalopathy findings from amplitude-integrated EEG (aEEG) or standard EEG</td>
<td><strong>Selective head cooling</strong> was started within 6 hours of birth, to the target rectal temperature of 34-35°C for 72hrs, followed by rewarming of no more than 0.5°C per hr until normal temperature range (35.5-37.5°C) (n=112)</td>
<td>Nursed under a radiant warmer with rectal temperature maintained at 36.8-37.2°C (Standard Care) (n=118)</td>
<td>18 months</td>
<td>Primary outcomes at 18 months: 1) Death 2) Death or severe disability 3) Death or severe disability among infants with intermediate aEEG 4) Death or severe disability among infants with severe aEEG 5) Severe neuromotor disability (GMFCS level 3-5) 6) Bayley MDI&lt;70 7) Bilateral cortical visual impairment Secondary outcomes: 8) Bayley PDI&lt;70 9) Bilateral sensorineural hearing loss 10) Epilepsy</td>
<td>1) OR: 0.81 (CI:0.47-1.41) p=0.48 2) OR: 0.61 (CI:0.34-1.09) p=0.10 3) OR: 0.97 (CI:0.26-0.87) p=0.02 4) OR: 1.8 (CI:0.49-6.4) p=0.51 5) OR: 0.54 (CI:0.25-1.17) p=0.12 6) OR: 0.66 (CI:0.32-1.36) p=0.27 7) OR: 0.52 (CI:0.19-1.39) p=0.22 8) OR: 1.47 (CI:0.37-5.84) p=0.72 9) OR: 0.98 (CI:0.37-2.28) p=1</td>
</tr>
<tr>
<td>Gluckman et al., 2005 (CoolCap Study)</td>
<td>Randomized Controlled Trial</td>
<td>1++</td>
<td>Newborn of ≥ 36 weeks gestation with clinical indicators of HIE, umbilical cord blood pH ≤ 7.0 or base deficit ≥ 16mmol/L during 1st hour after birth or Apgar Scores ≤5 at 10 mins</td>
<td><strong>Whole body hypothermia</strong> was started within 6 hours of birth, to the target esophageal temperature of 33.5°C together with the abdominal wall skin temperature monitoring for 72hrs, followed by automatic control of rewarming of increasing 0.5°C per hr until 36.5°C (n=102)</td>
<td>Nursed under a radiant warmer with rectal temperature maintained at 36.5-37.0°C (Standard Care) (n=106)</td>
<td>18-22 months</td>
<td>Primary outcomes at 18-21 months: 1) Death or moderate or severe disability Secondary outcome: 2) Death 3) Death or disability among infants with moderate encephalopathy 4) Death or disability among infants with severe encephalopathy 5) Bayley MDI&lt;70 6) Bayley PDI&lt;70 7) Disabling cerebral palsy 8) Blindness 9) Severe hearing impairment</td>
<td>1) OR: 0.52 (CI:0.29-0.89) p=0.01 2) OR: 0.55 (CI:0.30-1.00) p=0.08 3) OR: 0.55 (CI:0.3-1.01) p=0.09 4) OR: 0.59 (CI:0.32-1.10) p=0.24 5) OR: 0.78 (CI:0.39-1.53) p=0.18 6) OR: 0.93 (CI:0.47-1.83) p=0.39 7) OR: 0.78 (CI:0.38-1.65) p=0.2 8) OR: 0.50 (CI:0.16-1.54) p=0.2 9) OR: 0.77 (CI:0.17-3.54) p=0.47</td>
</tr>
</tbody>
</table>

1: Level of evidence as defined by Harris et al. (2001)
2: Only outcome measures related to the research questions of this review are extracted.
3: HIE = Hypoxic-ischemic encephalopathy
4: OR=Odd ratio, CI=Confidence interval
5: Source of funding: Olympic Medical
6: aEEG= amplitude-integrated Electroencephalophalogram
7: GMFCS=Gross Motor Function Classification System
<table>
<thead>
<tr>
<th>Bibliographic citation</th>
<th>Study type</th>
<th>Level of Evidence</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azzopardi et al., 2009 (TOBY study)</td>
<td>Randomized Controlled Trial</td>
<td>1++</td>
<td>Newborn of ≥ 36 weeks gestation with clinical indicators of HIE, umbilical cord, arterial, or capillary pH &lt; 7.0 or base deficit ≥ 16mmol/L or Apgar Scores ≤ 5 at 10 mins</td>
<td>Whole body hypothermia was started within 6 hours of birth, to the target rectal temperature of 33-34°C for 72hrs, followed by rewarming of increasing no more than 0.5°C per hr until 37.0±0.2°C</td>
<td>Nursed under a radiant heaters or in incubators which were servo-controlled according to the abdominal skin temperature with rectal temperature maintained at 37.0±0.2°C (Standard Care)</td>
<td>18 months</td>
<td>Primary at 18 months: 1) Death and severe neurodevelopmental disability Secondary at 18 months: 2) Death 3) Survival without neurologic abnormality 4) Multiple neurodevelopmental disability 5) Bayley MDI&lt;70 6) Bayley PDI&lt;70 7) GMFCS score 3-5 8) Cerebral Palsy 9) Hearing loss not corrected by aids 10) No useful vision</td>
<td>1) OR: 0.73 (CI:0.48-1.14) p=0.17 2) OR: 0.93 (CI:0.57-1.52) p=0.95 3) OR: 2.0 (CI:1.26-3.19) p=0.003 4) OR: 0.54 (CI:0.29-1.01) p=0.05 5) OR: 0.61 (CI:0.34-1.09) p=0.09 6) OR: 0.60 (CI:0.34-1.09) p=0.09 7) OR: 0.56 (CI:0.31-1.02) p=0.06 8) OR: 0.55 (CI:0.32-0.94) p=0.03 9) OR: 0.53 (CI:0.15-1.85) p=0.31 10) OR: 0.61 (CI:0.24-1.56)</td>
</tr>
<tr>
<td>Simbruner et al., 2010 (neo.nEURO)</td>
<td>Randomized Controlled Trial</td>
<td>1++</td>
<td>Newborn of ≥ 36 weeks gestation with clinical indicators of HIE, umbilical cord blood pH or any arterial pH of &lt;7.0 or base deficit ≥ 16mmol/L within 60 mins or Apgar Scores &lt;5 at 10mins, without congenital abnormality, encephalopathy findings from amplitude-integrated EEG (aEEG) or standard EEG</td>
<td>Whole body hypothermia was started within 6 hours of birth, to the target rectal temperature of 33.5°C for 72hrs, followed by rewarming of increasing no more than 0.5°C per hr to reach normal rectal temperature (n=62)</td>
<td>Nursed under a radiant heaters with rectal temperature maintained at 37.0°C (range : 36.5-37.5) (Standard Care)</td>
<td>18-21 months</td>
<td>Primary at 18-21 months: 1) Death or severe disability Secondary at 18-21 months: 2) Death 3) Death or severe disability in moderate HIE 4) Death or severe disability in severe HIE 5) DQ² of&lt;2SD 6) Disabling cerebral Palsy 7) Bilateral cortical visual deficit 8) Severe hearing loss</td>
<td>1) OR: 0.21 (CI:0.09-0.54) p=0.01 2) OR: 0.48 (CI:0.21-1.13) p=0.92 3) OR: 0.31 (CI:0.08-1.28) p=0.103 4) OR: 0.17 (CI:0.05-0.57) p=0.045 5) OR: 0.21 (CI:0.06-0.67) p=0.09 6) OR: 0.16 (CI:0.04-0.61) p=0.07 7) OR: 0.61 (CI:0.04-10.38) 8) OR: 0.01</td>
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</tbody>
</table>

1: Level of evidence as defined by Harris et al. (2001)
2: Only outcome measures related to the research questions of this review are extracted.
3: HIE= Hypoxic-ischemic encephalopathy
4: SD=Standard Deviation
5: OR=Odd ratio, CI=Confidence interval
6: GMFCS=Gross Motor Function Classification System 7: DQ= Developmental quotient 8: aEEG= amplitude-integrated Electroencephalogram
<table>
<thead>
<tr>
<th>Bibliographic citation</th>
<th>Study type</th>
<th>Level of Evidence</th>
<th>Patient Characteristics</th>
<th>Intervention(s)</th>
<th>Comparison</th>
<th>Length of follow up</th>
<th>Outcome measures</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al., 2010</td>
<td>Randomized Controlled Trial</td>
<td>1++</td>
<td>Newborn of ≥ 37 weeks gestation with clinical indicators of HIE, cord blood gas pH &lt; 7.0 or base deficit ≥ 16 mmol/L or Apgar Scores ≤ 3 at 1 min and ≤ 5 at 5 min</td>
<td>Selective head cooling was started within 6 hours of birth, to the target rectal temperature of 34.5 to 35°C for 72hrs with nasopharyngeal temperature monitoring as reference, maintained at 34±0.2°C, followed by spontaneous rewarming in room temperature to normal temperature. (n=100)</td>
<td>Nursed under a radiant heater with rectal temperature maintained at 36 to 37.5°C (Standard Care) (n=94)</td>
<td>18 months</td>
<td>Primary at 18 months: 1) Death or severe disability 2) Death 3) Severe disability Secondary at 18 months: 4) Death or severe disability on infants with moderate to severe HIE 5) Death or severe disability on infants with moderate HIE 6) Survival with severe disability on infants with moderate to severe HIE 7) Survival with severe disability on infants with moderate HIE 8) DQ of total infants &lt; 70 9) DQ of infants with moderate to severe HIE</td>
<td>1) OR: 0.47 (CI: 0.26-0.84) p=0.01 2) OR: 0.62 (CI:0.32-1.2) p=0.16 3) OR: 0.4 (CI:0.17-0.92) p=0.03 4) OR: 0.42 (CI:0.22-0.8) p=0.01 5) OR: 0.33 (CI:0.16-0.85) p=0.02 6) OR: 0.36 (CI:0.15-0.87) p=0.02 7) OR: 0.49 (CI:0.18-1.33) p=0.21 8) OR: 0.22 (CI:0.07-0.7) p=0.1 9) OR: 0.21 (CI:0.06-0.69) p=0.01</td>
</tr>
<tr>
<td>Jacobs et al., 2011</td>
<td>(ICE Trial)</td>
<td>Randomized Controlled Trial</td>
<td>Newborn of ≥ 35 weeks gestation with clinical indicators of HIE, metabolic acidosis with cord pH &lt;7.0; an arterial, venous, or capillary pH&lt;7.0 or base deficit ≥ 12 mmol/L within 60 mins of birth or Apgar Scores ≤ 5 at 10 min</td>
<td>Whole body hypothermia was started within 6 hours of birth, by applying refrigerated gel packs across the chest and/or under the head and shoulders to the target rectal temperature of 33.5°C for 72hrs, followed by rewarming 0.5°C every 2 hours over 8 to 12 hours (n=110)</td>
<td>Nursed under a radiant warmer with core temperature maintained at 37°C (Standard Care) (n=111)</td>
<td>24 months</td>
<td>Primary at 24 months: 1) Death or major disability 2) Death or major disability on moderate encephalopathy at assessment for eligibility 3) Death or major disability on severe encephalopathy at assessment for eligibility Secondary at 24 months: 4) Death 5) Major sensorineural disability 6) Neuromotor delay 7) Cerebral palsy 8) GMFCS’ disability level 2-5 9) Bayley MDI&lt;2SDs 10) Bayley PDI&lt;2SDs 11) Legal blindness 12) Defeasc requiring amplification Survival free of any disability</td>
<td>1) OR: 0.54 (CI: 0.31-0.94) p=0.03 2) OR: 0.37 (CI: 0.17-0.80) p=0.16 3) OR: 0.63 (CI:0.13-2.91) 4) OR: 0.53 (CI:0.29-0.95) p=0.04 5) OR: 0.73 (CI:0.37-1.46) p=0.37 6) OR: 1.01 (CI:0.52-2.14) p=0.7 7) OR: 0.89 (CI:0.42-1.89) p=0.77 8) OR: 0.97 (CI:0.42-2.25) p=0.95 9) OR: 0.91 (CI:0.40-2.03) p=0.81 10) OR: 0.78 (CI:0.34-1.78) p=0.55 p=0.99 11) OR: 0.73 (CI:0.09-5.32) p=0.75 12) OR: 2.24 (CI:1.21-4.14) p=0.01</td>
</tr>
</tbody>
</table>

1: Level of evidence as defined by Harris et al. (2001)  
2: Only outcome measures related to the research questions of this review are extracted.  
3: HIE= Hypoxic-ischemic encephalopathy  
4: OR=Odd ratio, CI=Confidence interval  
5: GMFCS=Gross Motor Function Classification System  
a: P value for interaction between treatment group and stage of encephalopathy at assessment for eligibility
### Appendix F: Table of Evidence on Adverse Effects

**Table 3**  
Table of Evidence on Adverse effects

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>Bibliographic citation</th>
<th>Minor cardiac arrhythmia (sinus bradycardia)</th>
<th>Hypotension (MAP$^&lt;$40mmHg)</th>
<th>Prolong QT interval</th>
<th>Coagulopathy (clinical bleeding + abnormal clotting)</th>
<th>Platelet count $&lt;$100000 per $\mu$L(^\S)</th>
<th>Raised liver enzymes concentration (AST$&gt;$200U/L or ALT$&gt;$100U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluckman et al., 2005 (CoolCap Study)</td>
<td>OR =10 (CI: 1.26-79.40)</td>
<td>OR=1.16 (CI: 0.69-1.95) p=0.6</td>
<td>----</td>
<td>OR=1.37 (CI: 0.68-2.76) p=0.38</td>
<td>OR=1.68 (CI: 0.93-3.02) p=0.1</td>
<td>OR=0.54 (CI: 0.32-0.92) p=0.02</td>
<td></td>
</tr>
<tr>
<td>Shankaran et al., 2005 (NICHD study)</td>
<td>OR=2.10 (CI: 0.19-23.52)</td>
<td>OR=1.42 (CI: 0.81-2.50) (Treated with vasopressor)</td>
<td>----</td>
<td>OR=1.68 (CI: 0.76-3.70) p=0.51</td>
<td>----</td>
<td>OR=1.37 (CI: 0.67-2.83)</td>
<td></td>
</tr>
<tr>
<td>Azzopardi et al., 2009 (TOBY study)</td>
<td>OR=2.74 (CI: 0.71-10.5)</td>
<td>OR=0.71 (CI: 0.41-1.23) p=0.22</td>
<td>----</td>
<td>OR=0.87 (CI: 0.56-1.35) p=0.51</td>
<td>OR=1.40 (CI: 0.90-2.16) p=0.15</td>
<td>----</td>
<td></td>
</tr>
<tr>
<td>Simbruner et al., 2010 (neo.nEURO)</td>
<td>OR=0.75 (CI: 0.16-3.50)</td>
<td>OR=1.42 (CI: 0.70-2.88) p=0.421</td>
<td>----</td>
<td>OR=0.59 (CI: 0.24-1.50) p=0.339</td>
<td>OR=0.70 (CI: 0.32-1.51) p=0.303</td>
<td>OR=0.72 (CI: 0.31-1.64) p=0.449</td>
<td></td>
</tr>
<tr>
<td>Zhou et al., 2010</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>OR=3 (CI: 0.65-16.62) p=0.28</td>
<td></td>
</tr>
<tr>
<td>Jacobs et al., 2011 (ICE Trial)</td>
<td>----</td>
<td>OR= 0.96 (CI: 0.57-1.64) p=0.89 (Treated with inotropes)</td>
<td>OR= 3.08 (CI: 1.43-6.62) p=0.006</td>
<td>OR= 1.81 (CI: 0.84-3.92) p=0.13</td>
<td>OR= 1.29 (CI: 0.76-2.19) p=0.41</td>
<td>OR= 0.65 (CI: 0.37-1.14) p=0.14</td>
<td></td>
</tr>
</tbody>
</table>

# Mean Arterial Pressure  
\( \S \mu\text{L} = \text{microliter} \left(10^{-6} \text{ liters}\right)\)  
\(^\wedge\) OR = Odd ratio, CI = Confidence interval, p = p-value  
*---- = not reported
### Appendix G: Table of Quality Assessment Table of Selected RCTs (Internal Validity)

Table 4
Quality Assessment Table of Selected RCTs (Internal Validity)

<table>
<thead>
<tr>
<th>Study</th>
<th>Clearly Focused Question</th>
<th>Random Allocation</th>
<th>Adequate Concealment</th>
<th>“Blind” about treatment</th>
<th>Treatment and control group are similar at starts</th>
<th>Only Difference is Treatment</th>
<th>Valid Measurement of Outcomes</th>
<th>Drop Out Rate</th>
<th>Intention to Treat Analysis</th>
<th>Comparable Results for all sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluckman et al., 2005 (CoolCap Study)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 7.1%, C: 6.7%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shankaran et al., 2005 (NICHD study)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 0%, C: 2.8%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Azzopardi et al., 2009 (TOBY study)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 0.6%, C: 0.6%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Simbruner et al., 2010 (neo.nEURO)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 14.5%, C: 7.9%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhou et al., 2010</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 16%, C: 19%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacobs et al., 2011 (ICE Trial)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Dose not apply</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>HT: 6.4%, C: 19.8%</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Yes, No, Can’t say, Dose not apply
HT=Hypothermia Group
C=Control Group
### Appendix H: Table of Quality Assessment Table of Selected RCTs (Overall Assessment)

#### Table 5
Quality Assessment Table of Selected RCTs (Overall Assessment)

<table>
<thead>
<tr>
<th>Study</th>
<th>Bias Minimized</th>
<th>Direction of Bias</th>
<th>Effect due to Intervention</th>
<th>Results Applicable to Target Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gluckman et al., 2005 (CoolCap Study)</td>
<td>+</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Shankaran et al., 2005 (NICHD study)</td>
<td>+</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Azzopardi et al., 2009 (TOBY study)</td>
<td>+</td>
<td><strong>Incomplete outcome data with short-term outcomes nearly complete</strong> (62/64 cooled and 63/65 control infants), but follow-up data was incomplete (53/64 (83%) of cooled and 58/65 (89%) of control infants)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Simbruner et al., 2010 (neo.nEURO)</td>
<td>+</td>
<td><strong>Incomplete outcome data with short-term outcomes nearly complete</strong> (62/64 cooled and 63/65 control infants), but follow-up data was incomplete (53/64 (83%) of cooled and 58/65 (89%) of control infants)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zhou et al., 2010</td>
<td>+</td>
<td><strong>Outcome data (both short and long term) incomplete on 16% of those cooled and 22% of those who received standard care. Of those infants for whom short-term data were reported, follow-up data were complete (93% of cooled and 94% of control infants followed up, including some infants whose follow-up was by telephone or at local paediatrician)</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Jacobs et al., 2011 (ICE Trial)</td>
<td>+</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(+=High quality, +=Acceptable, 0=unacceptable)
## Appendix I: Gantt Chart for the Intervention

<table>
<thead>
<tr>
<th>Gantt Chart for the Intervention</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14</td>
</tr>
<tr>
<td>Form a working committee and train program facilitators</td>
<td></td>
</tr>
<tr>
<td>Pilot testing</td>
<td></td>
</tr>
<tr>
<td>Revise the program based on pilot testing</td>
<td></td>
</tr>
<tr>
<td>Prepare for the program to “kick off”</td>
<td></td>
</tr>
<tr>
<td>Full Implementation</td>
<td></td>
</tr>
<tr>
<td>Evaluate the program</td>
<td></td>
</tr>
</tbody>
</table>
Appendix I-Data Collection Form
(Fill in upon discharge)

Admission Date: ____________________________

Date of Birth: ____________________________

Maturity: ____________________________

Place of Birth: ____________________________

Diagnosis: ____________________________

Therapeutic hypothermia applied: Yes/No ____________________________

Outcome: ____________________________

Remarks: ____________________________
# Appendix J- Staff Satisfaction Questionnaire

Please tick the appropriate answer.

<table>
<thead>
<tr>
<th>1. The guideline is easy to understand</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. The video used for training is useful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. There is adequate training time before implementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. The intervention is properly arranged</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The intervention is beneficial to the neonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. There are enough equipment for use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. The workload is affordable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Overall, you are satisfied with this intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Any other comments or suggestions on this intervention?

__________________________________________________________________
__________________________________________________________________
__________________________________________________________________
### Appendix K - Parents' Satisfaction Questionnaire

Please tick the appropriate answer.

<table>
<thead>
<tr>
<th>1. The explanation provided by the nurses and doctors is easy to understand</th>
<th>Strongly Disagree</th>
<th>Disagree</th>
<th>Neutral</th>
<th>Agree</th>
<th>Strongly Agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. The explanation provided by the nurses and doctors is adequate</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>3. The nurses and doctors are knowledgeable and helpful in answering the enquiries about the intervention</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>4. The educational leaflet is easy to understand</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>5. The educational leaflet is informative</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>6. The intervention is properly arranged</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>7. The intervention is beneficial to your baby</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
<tr>
<td>8. Overall, you are satisfied with this intervention</td>
<td>Strongly Disagree</td>
<td>Disagree</td>
<td>Neutral</td>
<td>Agree</td>
<td>Strongly Agree</td>
</tr>
</tbody>
</table>

Any other comments or suggestions on this intervention?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
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